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Interaction between Selenium and Methylmercury

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The available data on the influence of selenium on the toxicity of methylmercury and of methylmercury on selenium as a nutrient and toxic agent are reviewed. Selenium as selenite has a relative protective effect on acute and subacute toxicity of methylmercury in the rat and the quail. The protective mechanism is far from clear. Of special interest is the fact that selenium-treated animals may remain unaffected, even when they have attained tissue mercury levels otherwise associated with toxic effects. Selenite causes some increase of tissue mercury levels in methylmercury-exposed animals. On the other hand, methylmercury induces a remarkable enhancement of organ concentrations of selenium in animals given selenite. The interaction between selenium and methylmercury is in many ways different from that between selenium and inorganic mercury, and also from that between selenium and other metals. Due to the considerable interspecies differences in the toxicity of methylmercury, the available data do not allow conclusions on interactions in man. Practical implications of a possible protective effect of selenium on methylmercury toxicity in humans are discussed.

Introduction

As long ago as 1938, Moxon (*1*) reported that arsenic counteracted the toxic effects of seleniferous grain. Since then, interaction has been demonstrated between selenium on the one hand, and tungsten, germanium, antimony, copper, cadmium, tellurium, thallium, and silver on the other (*2*).

In 1967, Parizek and Ostadalova (*3*) demonstrated that selenite (and, to a lesser extent, selenomethionine) dramatically decreased the acute nephrotoxicity of mercuric mercury in rats, provided that the selenium compound was given after the mercury compound. If, on the other hand, selenite was given before mercuric mercury, an increased mortality was observed in males, which was also the case if mercuric mercury and dimethylselenide or trimethylselenonium ion were administered (*4*). In chronic exposure in rats, selenite reduced the toxicity of mercuric mercury (*5, 6*), while mercuric mercury did not affect the toxicity of selenite (*7*).

In 1972, Ganther et al. (*8*) demonstrated that selenium decreased the toxicity of methylmercury. This review will summarize the available information on the effect of selenium compounds on the toxicity of methylmercury, and on the impact of methylmercury on selenium compounds as toxic agents and nutrients.

Methylmercury

There are very great differences toxicologically between different chemical forms of mercury (*9*). In man, methylmercury (CH_3Hg^+) is the mercury compound having received most interest lately, due to larger-scale outbreaks of poisoning caused by treated seed (*10*) and contaminated fish (*11*). Methylmercury is degraded only to a minor extent into mercuric mercury (Hg^{2+}). However, there is a considerable interspecies difference in degradation rate. In rats, the formation of mercuric mercury is sufficient to cause kidney damage of the type seen after administration of mercuric mercury as such (*12*). In man the degradation is probably very limited. The biochemical basis for toxic effects is not known, but interaction with thiols is probable.

The typical noxious effect of methylmercury is neurotoxicity, which appears with a latency of days to weeks after a single dose. However, the neurotoxicity differs between different species. Thus, the lesions in man are located in the central nervous system, while in the rat the peripheral nervous system is damaged first (*13*). In birds, central

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nervous system lesions occur, but the microscopical picture is different from that seen in man (*14*). Methylmercury is fetotoxic; mercuric mercury is not. Methylmercury is excreted into milk, mercuric mercury to a much less extent. Also, there are indications that methylmercury may cause effects on the genetic material. All these circumstances must be considered when interaction is discussed.

Selenium

In 1944, Schwarz (*15*) demonstrated that selenium is an essential nutrient in rats. Recently, it was shown to be essential in humans as well (*16*). Glutathione peroxidase, which handles lipoperoxides, is a selenoenzyme. The deficiency syndrome differs considerably between different species (*17–21*). The requirement is dependent upon intake of vitamin E, polyunsaturated fatty acids, and sulfuramino acids. In different species the requirements range 0.04–0.2 mg Se/kg food. The requirements in man is not known (*22*). Little is known about the chemical forms of selenium in foods and tissues; selenoamino acids, selenite and selenate occur. It is well established that the biological availability varies. Selenium in tuna and other fish has a low availability. Diplock (*20*) proposed the following metabolism, based mainly on studies in rats. Selenomethionine and selenate (SeO_4^-) are metabolized into selenite (SeO_3^{2-}), which is in turn transformed into the selenotrisulfide derivative of glutathione (GSSeSG), and further transformed into the selenopersulfide (GSSeH), from which selenide ion (Se^{2-}) is formed. This is methylated into trimethylselenonium ion [$(CH_3)_3Se^+$], which is excreted in urine. When excessive amounts of selenium are administered, dimethylselenide, $(CH_3)_2Se$, is formed and exhaled.

Selenium is a toxic element. The lesions induced vary considerably between different chemical forms of selenium and different species. It may affect the central nervous system. In general, levels corresponding to 5–10 mg Se/kg food are toxic (*20*). The biochemical basis for selenium toxicity has not been established, but possible consequences of uncontrolled reactions with thiols are numerous. Teratogenicity has been demonstrated in chicks.

Interaction of Selenium with Methylmercury Toxicity

In selenium- and vitamin E-deficient rats given methylmercury in the drinking water (1-25 mg Hg/l.), Ganther et al. (*8*) reported that 0.5 mg Se as selenite/kg food caused an increase of weight gain and a decrease (or at least a postponement) of mortality during a 6-week experiment. Similar results (and in addition an effect on neurological signs) in nondeficient rats have been reported by other authors feeding 10–40 mg Hg as methylmercury and 0.6–5 mg Se as selenite/kg food for 8–70 days (*23–27*).

Ohi et al. (*27*) fed rats methylmercury (20 mg Hg/kg food) and either selenite or selenium as present in tuna (0.5–1.5 mg Se/kg food). The tuna provided some protection. However, selenite was more efficient. Protein quantity and quality as well as food intake may have affected the results.

Potter and Matrone (*25*) reported that 10 mg Hg as methylmercury/kg food afforded protection from the negative effect on weight gain caused by feeding rats 5 mg Se as selenite/kg food.

The methylmercury exposures employed in these rat experiments were high. Chronic studies have indicated that some toxic effects of methylmercury occur already in the interval 0.5–2.5 mg Hg as methylmercury/kg food (*28*).

Ganther and Sunde (*29*) showed that addition of selenite to a diet decreased methylmercury-induced (20 mg Hg/kg food) mortality in Japanese quail. Increasing the selenium level from 0.1 mg/kg (in basal diet) to 6 mg/kg caused a prolongation of 50% mortality from 4 to 14 weeks. Also, there was a flattening of the dose–response curves. The preventive effect of selenite on methylmercury-induced mortality in quail has later been verified by other authors (*30, 31*). As low dietary levels as 0.05–0.1 mg Se as selenite/kg food gave some protection against 30 mg Hg as methylmercury/kg (*32*). Vitamin E provided additional protection, probably more pronounced when selenium levels were low than when they were high.

Ganther et al. (*8*) found that quail given 20 mg Hg as methylmercury/kg in food containing 17% tuna survived longer than quail given methylmercury in a corn-soy diet. The tuna diet contained 0.7 mg Se/kg, the corn-soy diet 0.4 mg/kg. The quail in both groups showed symptoms of methylmercury poisoning, but 50% mortality was reached after 6 weeks in the tuna group, and after 7 weeks in the corn-soy group (*29*). The food intake in different groups was not reported. In quail fed 10 mg Hg as methylmercury/kg food, a difference of 5 weeks has been stated between 50% mortality in a tuna and a corn-soy group. Still, 100% mortality occurred in a tuna group after 47 weeks of feeding (*29*). It was found that 1 mg Hg as methylmercury/kg in a tuna diet caused no mortality even after 47 weeks. No titration of a protective effect after long-time feeding has been reported. Selenium as selenite seemed to be more effective than selenium in tuna (prolongation of 50% mortality 1 vs. 5 weeks at similar selenium levels).

In chicks, 20 mg Hg as methylmercury/kg food caused considerably less mortality than in quail (*31*). Addition of 8 mg Se as selenite/kg food possibly provided some protection, but both methylmercury and selenite decreased weight gain, and the effect of both compounds was additive. The level of methylmercury in the food was high; growth retardation has been shown in one strain of chicks already at 2.6 mg Hg as methylmercury/kg food, although there was a considerable inter-strain difference (*33*).

In a brief publication, Froseth, Piper, and Carlson (*34*) mentioned an experiment in pigs fed selenite at levels of 0.1–5 mg Se/kg food for 6-7 weeks. After 5 weeks of exposure a single dose of 7 mg Hg as methylmercury/kg body weight was given. In pigs fed low selenium levels, methylmercury was reported to induce signs of selenium deficiency; high levels of selenium had a preventive effect on methylmercury toxicity.

In a chronic feeding experiment, slight neurological signs and microscopical central nervous system and liver lesions were found in cats fed tuna containing about 0.5 mg Hg/kg for 7–11 months (*35, 36*). Mercury in tuna is known to be almost entirely methylmercury. The selenium content of the tuna was not determined. It is reasonable, though, to assume a level of at least 1 mg Se/kg. It is interesting to compare these results with similar experiments performed with freshwater pike by Charbonneau et al. (*37*). In a two-year experiment, the lowest level of methylmercury that induced toxic effects was 0.8 mg Hg/kg in a diet containing 0.1 mg Se/kg food. Even if the toxicity in the cats in the first experiment is not fully convincing, the comparison of the two studies illustrates the need for further research.

Little information is available concerning effects of selenium on methylmercury toxicity of offspring. Ganther and Sunde (*29*) found some protective effect of tuna against early mortality among offspring of methylmercury-exposed quail. No data have been reported regarding effects of methylmercury on selenium-induced fetotoxicity or of selenium on the genotoxic effect of methylmercury.

Possible Mechanisms of Interaction

There are numerous possible mechanisms for the interaction between methylmercury and selenium. In principle, the interaction may be direct or indirect (or a combination). A direct interaction may involve formation of complexes between some chemical form of selenium and some chemical form of mercury, the simplest possibility being HgSe, but many different complexes may be anticipated. Also, selenium and mercury may compete for binding sites in proteins (most probably thiols) or other compounds. A competition may occur on the "receptor sites" where mercury and selenium exert their toxic effects, but a complex binding or a competition at other binding sites may also affect the metabolism (absorption, distribution, biotransformation or excretion) which may affect the "receptor site" concentration secondarily. In the case of selenium, corresponding effects may be exerted on the "receptor sites" for its function as an essential nutrient.

An indirect interaction may involve effects by one compound on any metabolic function affecting the other. There are numerous possibilities. Enzyme systems performing biotransformation of one compound may be affected by the other, or membrane function may be impaired by one compound, causing an alteration of membrane passage of the other. Of course, this eventually results in an increase or decrease of the toxic form of the compound at the "receptor sites." In the case of methylmercury, degradation into mercuric mercury is of special interest. As for selenium, the well-known interdependence between selenium, vitamin E, polyunsaturated fatty acids, and sulfuramino acids (*20*) offers many possibilities.

Observations Bearing on the Mechanism of Interaction

In this section, reported data supporting the different possible mechanisms will be reviewed. This information pertains mainly to the metabolism and binding of methylmercury and selenium.

Absorption

There are no reports on studies on the gastrointestinal absorption of methylmercury in the absence or presence of selenium. The absorption is almost complete in animals during regular feeding (*38*). Thus, only a negative effect of selenium should be expected. Published data on levels of mercury in organs do, however, indicate that at least no major effect should be anticipated in quail or rat (*24–27, 30, 31, 68*).

Nor have studies on effects of methylmercury on absorption of selenium appeared. The absorption of selenite is almost complete (*19*). As data on effects of methylmercury on tissue levels of selenium in rats clearly indicate an increase, no major effect on selenite absorption should be expected, at least in rats (*24, 27*).

Retention and Excretion

Combined single parenteral exposure of rats to mercuric mercury and selenite or selenate causes an increase of whole-body retention of mercury as compared to what happens in animals not treated with selenium (*3, 39*). The whole-body elimination rate (*39*) and the elimination of mercury in urine and feces are decreased (*4, 40, 41*).

Stillings et al. (*26*) found a slight decrease of fecal and urinary excretion of mercury in rats fed 15 mg Hg as methylmercury and 0.6 mg Se as selenite/kg food for 4 weeks as compared to animals not fed additional selenium. The total mercury retention was 2% higher in selenium-treated animals. This is in accordance with the observation of limited effects of selenium on tissue mercury levels after administration of methylmercury.

Arsenic increases the elimination of selenium in bile (*42*). Mercuric mercury has no corresponding effect (*7*). Thallium and mercuric mercury decrease the elimination of selenium in urine (*7*). As mentioned above, exhalation of dimethylselenide is an important elimination route when exposure to selenium is excessive. Single injections of cadmium, thallium, and mercuric mercury reduce this exhalation of selenium in the rat (*4, 7*).

No data have been reported on the whole-body retention or excretion of selenium during treatment with methylmercury. However, data on tissue selenium levels (*vide infra*) indicate that an increase of retention and decrease of excretion may occur in the rat.

Parizek et al. (*43*) showed that selenite administration decreased the passage of mercuric mercury into milk in rats. No corresponding studies have been performed with methylmercury.

Administration of mercuric mercury to rats decreased the passage of selenium administered as selenite into milk, thus lowering the selenium content of sucklings (*44*). It is not known whether this applies also to methylmercury administration.

Distribution and Biotransformation

Selenium administration causes remarkable effects on tissue distribution of mercuric mercury in rats. When mercuric mercury is administered in single injections, selenite, selenate and selenomethionine cause a marked decrease in kidney mercury levels, while levels in liver and muscle increase (*4, 45*). In blood, mercury is redistributed from cells to plasma (*40, 46, 47*). The distribution pattern is dependent on the dose of selenium injected, the most pronounced changes occurring at molar Se/Hg ratios about unity (*40*).

However, when selenium and mercuric mercury were administered repeatedly to rats (*5*) and mice (*48*), increased mercury levels in kidney were found instead.

Data on effects of selenium on total mercury levels in tissue after exposure to methylmercury are shown in Table 1. Detailed information is available only for quail, chicks, and rats. Exposures to methylmercury were high and generally short.

Total mercury levels in tissues in animals repeatedly exposed to methylmercury were not greatly affected by selenium administration; in no study did the effect exceed a factor 2. The methylmercury exposure caused a decrease of food intake by chicks and rats (but not by quail). However, this did not affect the mercury accumulation. There were no major differences between animals receiving selenium as selenite or as present in tuna.

Rats treated with selenite and sacrificed soon after their last administration of methylmercury had higher brain mercury levels than animals not treated with selenium (*23, 49*). In animals sacrificed 7 days after the last treatment, a decrease of brain methylmercury levels had occurred in selenite-treated animals, while an increase in these levels had taken place in animals not treated with selenite (*23*). It is well known that there is a delay in distribution of methylmercury to the central nervous system of the rat (*38*). This delay may be reduced by simultaneous administration of the chelating agent dimercaprol (BAL). Thus, selenite may have a BAL-like effect, causing a more rapid turnover of methylmercury in the brain.

Although no major effects attributable to selenium were noted on tissue mercury levels, it is interesting that, at similar brain mercury levels, selenium-treated quail may have a low mortality while quail not so selenium-treated have a high mortality (*30*). This indicates a less toxic action by the methylmercury present in the brain of selenium-treated animals. On the other hand, Ganther and Sunde (*29*) reported that poisoned quail treated for 47 weeks, with 10 mg Hg as methylmercury and 0.7 mg Se in tuna/kg food, had 9 mg Hg/kg brain, which is well established to be a toxic level in several species of animals when they are not treated with selenium (*50*). This clearly indicates the need for further chronic studies using lower methylmercury exposures.

Considerable total mercury levels in brain have also been reported in selenium-treated non-poisoned rats (*23, 27*).

Administration of mercuric mercury in single (*7, 45*) or repeated injections (*48*), or by chronic feeding (*5*), causes increased levels of selenium in liver, kidney and blood in rats and mice injected with

Table 1. Effect of selenium on tissue total mercury (Hg) levels and of methylmercury on tissue total selenium (Se) levels.

	Exposure			Mercury accumulation[c]				Selenium accumulation[d]				
Species	Time, days	Hg, mg/kg food[a]	Se, mg/kg food[a, b]	Brain	Liver	Kidney	Muscle	Brain	Liver	Kidney	Muscle	Reference
Japanese quail	28	20	0.7 T[e]	1.0	0.9	1.1	0.9	—	—	—	—	(*68*)
	35	20	5	1.1	1.2	1.5	—	—	—	—	—	(*30*)
	23	20	8	1.6	1.0	—	1.0	—	—	—	—	(*31*)
Chicks	25	20	8	1.0	0.7	—	0.6	—	—	—	—	(*31*)
Rats	8	10 mg/kg-day[f]	0.5 mg/kg-day[f]	1.7[g]	1.0[g]	1.0[g]	—	—	—	—	—	(*23*)
	28	25	3	—	1.8	—	—	10	1.0	2.0	1.2	(*24*)
	21	10-40	5	—	1.0-1.7	0.6-1.0	—	—	—	—	—	(*25*)
	14	25	0.6	0.7	1.1	0.5	0.8	—	—	—	—	(*26*)
	70	20	1.0 T	1.5	1.1	1.5	—	2.3	4.8	3.7	—	(*27*)
	70	20	1.0	1.4	1.2	1.4	—	4.2	4.0	4.2	—	(*27*)
Pigs[h]	42-49	7 mg/kg (single dose)	5[i]	<1	<1	<1	<1	—	<1	<1	<1	(*34*)

[a] If not indicated otherwise.
[b] T denotes that Se was given as tuna; in other studies it was given as selenite.
[c] Level in group given Hg and Se/level in group given Hg only.
[d] Level in group given Se and Hg/level in group given Se only.
[e] Level in control group ("low Se") 0.4 mg Se/kg. In most other cases, Se levels in "control group" were not given.
[f] Subcutaneous administration.
[g] Methylmercury levels.
[h] Scanty information.
[i] Se levels in "controls" 0.03–0.05 mg/kg.

selenite. As simultaneously levels of mercury in kidney were decreased, Magos and Webb (*45*) concluded that not all of the interaction was due to formation of selenium-mercury complexes. On the other hand, Groth et al. (*5*) noted particles containing mercury and selenium in kidney and reticuloendothelial cells, which they proposed consisted of HgSe. In this context it could be mentioned that tissues from workers exposed to elemental mercury had elevated levels of mercury and selenium (*51*, *52*). In liver, kidney, and possibly brain, the molar Se/Hg ratio was roughly unity.

In rats, methylmercury causes a severalfold increase in total selenium levels in tissue (Table 1). This effect is much greater than that of selenium on methylmercury. A very brief report on pigs (*34*) showed an effect in the opposite direction when a single oral dose of methylmercury was given.

Jernelöv et al. (*53*) fed minks with pike containing almost 6 mg Hg as methylmercury and 0.2 mg Se/kg (*54*) for up to 100 days. The animals showed no signs of poisoning. There was a considerable accumulation of mercury, in brain and muscle, almost entirely as methylmercury. In liver and kidney, a considerable fraction was inorganic mercury. There was no increase of selenium content in brain and muscle, while in liver and kidney selenium levels increased 3 and 2 times, respectively. The molar ratio Se/methylmercury was 0.3, 0.4, and 0.1 in liver, kidney, and brain, respectively. The corresponding ratios Se/Hg^{2+} were 0.3, 0.7, and 0.7, respectively.

Koeman et al. (*55*, *56*) reported high total mercury levels but low methylmercury contents in seals (presumably exposed almost entirely to methylmercury). The molar ratios Se/Hg were about unity in liver and brain. Ratios of 1–3 were noted in whale liver and brain (no data on levels of mercuric mercury were given). No Se/Hg correlation was noted in a few samples of marine birds.

Ohi et al. (*27*) exposed rats to methylmercury and selenite or selenium in tuna (Table 1). Levels of total mercury and methylmercury as well as selenium were analyzed in several organs. As mentioned above, there was a moderate increase of total mercury and a more pronounced increase of selenium in different organs. Selenium exposure had no clear effect on methylmercury levels in any organ. However, there was an increase of the content of mercuric mercury in brain, which then contained 10–23% of the total mercury. In liver and kidney there was only a marginal increase of mercuric mercury. Even if the fact that the brain is not the critical part of the nervous system in the rat is disregarded, the effects on demethylation seem too small to explain the protective effect of selenium. When animals treated with selenium as present in tuna were studied, no major differences between

these and selenite-treated animals could be observed. The molar ratio Se/methylmercury may be calculated at 0.1, 0.5, and 0.1 in brain, kidney, and liver, respectively (groups treated with selenite and selenium as present in tuna together). When the increase of selenium was used alone in the calculations, the ratios were of course even lower. The ratio Se/Hg^{2+} was 0.7, 0.9, and 0.5 in the same organs. When the increase of selenium caused by selenium exposure is considered alone, the ratio in the brain is 0.4.

The data quoted indicate a closer relation between selenium and mercuric mercury than between selenium and methylmercury. If this is not purely coincidental, it might indicate a possible mechanism for the protective effect of selenium against methylmercury toxicity, especially in light of the fact that both some experimental (*5*) and epidemiological (*51, 52*) human data indicate a parallel increase of levels of selenium and mercury upon exposure to inorganic mercury.

Transplacental Passage

Parizek et al. (*43*) showed that a single dose of selenite decreased the passage of mercuric mercury into fetuses. No studies have been devoted to methylmercury in this respect.

A dose of mercuric mercury decreased the passage of selenium administered as selenite into the fetus (*44*). There are no data on experimental studies on methylmercury. However, in this context it should be mentioned that a study in Minamata of umbilical cords, preserved at different times in relation to the outbreak of methylmercury poisoning, showed an increase of mercury content at the time of the outbreak but no corresponding effect on the selenium content (*57*). It is generally assumed that the Minamata area was contaminated not only with methylmercury but also with selenium. The study does not indicate any major effect of methylmercury on transplacental passage of selenium, at least not as reflected in the umbilical cord.

Subcellular Distribution

Chen, Whanger, and Fang (*47*) showed that selenite administration changed the subcellular distribution pattern of mercuric mercury in the rat. In liver, the crude nuclear, mitochondrial and microsomal fraction content increased while the soluble fraction content decreased. In kidney, mercury content of all fractions decreased. In a similar experiment employing a single injection of selenite and methylmercury, no significant effects on mercury distribution were noted (*49*). In seal liver Koeman et al. (*56*) found a molar Se/Hg (presumably mercuric mercury) ratio of unity at the subcellular level.

Protein Binding

Chen, Whanger, and Fang (*47*) studied the effect of selenite on protein binding of mercury administered as mercuric mercury in the soluble fraction from different rat organs. The mercury was diverted by selenite from low molecular weight proteins (presumably metallothionein) to large molecular weight proteins in the liver and kidney. Burk et al. (*46*) made similar findings in rat plasma. Their data indicated that selenium was bound to a sulfhydryl group and that mercury was attached to selenium. Selenite did not alter protein binding of methylmercury, which was bound to hemoglobin-containing and low molecular weight proteins other than metallothionein (*49*). Methylmercury has a very high affinity to selenohydryl groups (*58*).

Enzyme Effects

A few studies have been devoted to effects of the combination of selenium and mercury on enzyme activities. Wada et al. (*48*) found that administration of mercuric mercury to mice inhibited the selenoenzyme glutathione peroxidase in mouse kidney. Selenite administration offered complete protection. The authors suggested that the inhibition resulted from mercury complex binding of selenium. For silver, a corresponding inhibition of glutathione peroxidase has been shown (*20*). This is of special interest as silver induces a syndrome of selenium deficiency. Froseth, Piper, and Carlson (*34*) briefly reported that such deficiency was provoked by methylmercury in pigs fed a low selenium diet. However, the effects of methylmercury cannot be explained by induction of selenium deficiency as that syndrome is quite different from methylmercury poisoning. In studies of the enzyme glutathione reductase in rat and quail erythrocytes, Mykkanen and Ganther (*59*) noted some protective effect of food selenite against the inhibition by mercuric mercury added *in vitro*. Methylmercury did not cause any inhibition when given orally and only minor inhibition when added *in vitro*. Fang (*60*) recorded an induction by food selenium of a phenylmercury cleaving enzyme in rat liver. No effect was noted on ethylmercury cleavage. Methylmercury was not degraded at all.

In *in vitro* studies, Kasuya found that selenite (*61*) and vitamin E (*62*) inhibited the toxic effect of methylmercury and ethylmercury on nerve tissue cultures.

Concluding Comments

The data here reviewed indicate that selenite has a relative protective effect on methylmercury poisoning in quail and rat. However, the methylmercury exposures employed were high and the exposure time relatively short when the latency period in methylmercury poisoning and the slow elimination of methylmercury are considered. Metabolism and effects of methylmercury show remarkable interspecies variations. Rat and quail differ in several aspects from other animal species and man, and the available information does not allow conclusions on interactions in man.

Also, it has been claimed that selenium as present in tuna protects against methylmercury toxicity in quail and rat. Such protection has not been unequivocally shown; food intake as well as protein quantity and quality in the food might have affected the results. If tuna offers protection it is far from clear that selenium is the relevant factor. If the selenium in tuna is protective, the effect seems to be less than that of selenite. Further studies on this matter are urgent.

The mechanism(s) through which selenium provides protection against methylmercury poisoning is (are) far from clear. It is obvious, however, that the interaction of selenium and methylmercury is in many ways different from that of selenium and inorganic mercury, and also from that of selenium and other metals. Of special interest are the observations that selenium-treated animals may remain unaffected even when they have reached tissue mercury levels otherwise associated with toxic effects. There are some indications that selenium may have a BAL-like effect on methylmercury metabolism in the brain. Also, the remarkable parallel accumulation of selenium and mercuric mercury in tissues of methylmercury-treated animals deserves further study.

The selenium intake in humans from different areas has been estimated at 200 μg/day or less (*19, 21, 63*). This corresponds roughly to a level of 0.1 mg/kg or less in human diets. In the experimental work reviewed, selenite levels shown to affect methylmercury toxicity were 0.1-8 mg Se/kg. Thus, the exposure levels were high for the most part, especially as it is reasonable to assume that the biological availability of selenium in human diets is less than that of the selenite added to the experimental diets. In fact, the highest selenite levels employed were toxic. The selenium levels in the tuna diets were 0.7–1 mg Se/kg.

Also, it should be considered that the composition of the diets in the experimental groups compared may be critical. Dietary protein level and composition affect the toxicity of methylmercury (*26, 27*). Sulfuramino acids are known to affect the metabolism of methylmercury (*64*) and selenium (*20*). Levels of vitamin E also affect toxicity, possibly by saving selenium. Intakes of polyunsaturated fatty acids might also influence the results.

It is thus clear that the interesting findings hitherto reported must be further studied in experiments using other species, lower exposures to methylmercury and selenium for longer times, and controlled diets. Also, the lesions produced must be studied in greater detail; no reports on microscopical central nervous system changes have been published.

Ganther et al. (*8*) reported an interesting relation between selenium and mercury (almost entirely methylmercury) levels in tuna. The molar increase of selenium in a high-mercury batch as compared to a low-mercury one matched the mercury increase. Tuna might contain a built-in protective agent with regard to methylmercury toxicity. Further studies on this matter are urgent.

Marine fish is a major supply of selenium. Such fish usually have selenium levels of 1 mg/kg or more (*21*). The ratio between levels of mercury (methylmercury) and selenium in fish not significantly contaminated with mercury is 0.02–0.06 (*56*). The relation between selenium and mercury in mercury-contaminated marine fish other than tuna has not been reported. Fresh-water fish usually have selenium levels at or below 1 mg/kg (*65*). The relation between selenium and mercury has only been reported occasionally. It is interesting, though, that pike from northern Sweden (*54, 66*) and Canada (*37*) contained about 0.1 mg Se/kg, both in noncontaminated lakes (0.1 mg Hg/kg fish) and in severely contaminated waters [6–9 mg Hg (methylmercury)/kg]. In both cases, the contaminated fish were highly toxic for cats. This indicates that methylmercury may accumulate in dangerous concentrations in fresh-water fish without any corresponding, potentially protective, selenium increase.

Three major outbreaks of methylmercury poisoning in man have occurred. In Minamata, the poisoning was caused by marine fish (*67*). The area was also polluted by selenium (*29*). In Niigata, the methylmercury was carried by fresh-water fish (*11, 14*). In Iraq, methylmercury-treated seed was ingested by a rural population with low fish intake (*10*). The selenium supply is clear neither in Niigata nor in Iraq. The quantitative concepts of methylmercury toxicity in man, emerging from studies in Niigata and in Iraq, fit remarkably well and are not contradicted by data reported in nonpoisoned methylmercury-exposed humans from other areas (*10*). Data on the selenium supply in the Niigata area

and Iraq would, of course, be of great interest, particularly in the light of some differences in the clinical picture of poisoning between the Japanese cases and the Iraqi ones.

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